MICROFLUIDIC DEVICES FOR HIGH GRADIENT MAGNETIC SEPARATION

STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT

[0001] The invention resulted in part from work on U.S. Government contract 70NANB9H3012 and DARPA #MDA972-01-3-0001.

FIELD OF THE INVENTION

[0002] The invention relates generally to methods and apparatus for conducting analyses, particularly microfluidic devices for the detection of target analytes.

BACKGROUND OF THE INVENTION

[0003] Recent advances in molecular biology have provided the opportunity to identify pathogens, diagnose disease states, and perform forensic determinations by detecting a specific material in a sophisticated biological sample. In order to obtain higher sensitivity and reduce cost for such detections, there is a significant trend to reduce the sizes of the detection device. Thus, a number of microfluidic device have been developed, generally comprising a solid support with microchannels, utilizing a number of different wells, pumps, reaction chambers, and the like. EP 0637996 B1; EP 0637998 B1; WO96/39260; WO97/16835; WO98/13683; WO97/16561; WO97/43629; WO96/39252; WO96/15576; WO96/15450; WO97/37755; and WO97/27324; and U.S. Pat. Nos. 5,304,487; 5,071,531; 5,061,336; 5,747,169; 5,296,375; 5,110,745; 5,587,128; 5,498,392; 5,643,738; 5,750,015; 5,726,026; 5,35,358; 5,126,022; 5,770,029; 5,631,337; 5,569,364; 5,135,627; 5,632,876; 5,593,838; 5,585,069; 5,637,469; 5,486,335; 5,755,942; 5,681,484; and 5,603,351.

[0004] The quality and sensitivity of detections by these microfluidic devices depend on the amount of target analytes in a sample. When an analytes is rare in the sample, it is necessary and sometimes even critical to process the sample for the successful analysis and detection. Specifically, the target analytes may need to be concentrated, enriched, or purified from contaminants that will otherwise interfere with its analysis and detection. The paucity of efficient sample preparation and handling techniques remains a serious limitation for the routine use of microfluidic devices to analyze complex samples.

[0005] High gradient magnetic separation (HGMS) is a long established procedure for selectively retaining magnetic materials in a chamber or column disposed in a magnetic field. This technique has also been applied to non-magnetic targets, including biological materials, labeled with magnetic labels. The technique of HGMS is thoroughly discussed in U.S. Pat. Nos. 5,411,863 and 5,385,707. Briefly, a target analyte within a complex sample is labeled by a magnetic label through its association with a specific binding ligand that is conjugated to a coating on the particle. The target,analyte, thus coupled to a magnetic "label", is suspended in a fluid which is then applied to the chamber. In the presence of a magnetic gradient supplied across the chamber, the magnetically labeled target analyte is retained in the chamber; materials which do not have magnetic labels pass through the chamber. The retained target analyte can then be eluted by changing the strength of, or by eliminating, the magnetic field. The selectivity for a desired target material is supplied by the specific binding ligand conjugated to the magnetic particle.

[0006] Frequently, the chamber for HGMS contains a matrix of magnetically susceptibility material such as a steel wool or wire matrix. When a magnetic field is applied across the chamber, a high magnetic field gradient will be locally induced within the chamber in volumes close to the surface of the matrix, permitting the retention of fairly weakly magnetized particles. These designs have several disadvantages. First, unwanted materials are often trapped in crevices of the magnetically susceptible materials; second, because the interstitial spaces within the device and from device to device are nonuniform, the result produced are quite variable. Accordingly, improvements were made by packing small uniform ferromagnetic beads in a column to generate uniform interstitial spaces, and coating these beads to limit non-specific binding and help seal spaces that might trap unwanted materials (U.S. Pat. Nos. 5,711,871; 5,705,059; 5,543,289). Although these improvements greatly increased the efficiency and repeatability of separations, the improved columns cannot be optimized for rare target separation. Magnetic field gradients and insterstitial channel size are fixed by the bead size chosen. Smaller beads will produce stronger gradients but also smaller channel sizes. Even with relatively large beads (300 μm), the resulting ~30 μm channel size often requires pre-filtering, traps a significant amount of non-specific material and makes elution of target cells difficult.

[0007] It is an object in this invention to incorporate a miniaturized magnetic separation system in a microfluidic device for sample processing. It is also an object in the present invention to disclose a superior HGMS system that can produce a higher magnetic gradient and capture rare species in a sample as well as complexes that are weakly magnetized. It is yet another object of the present invention to provide a way of achieving efficient washing and sample processing and consequently a more sensitive and selective device for the detection of target analytes.

SUMMARY OF THE INVENTION

[0008] In a first aspect, an embodiment of the present invention is a microfluidic device comprising a solid support. The solid support comprises a sample inlet port a sample outlet port, and at least one microchannel comprising at least one section with walls comprising magnetic beads and an inner diameter devoid of beads. In an embodiment, the magnetic beads are embedded in the walls. In another embodiment, the magnetic beads are coated onto the inner surface of the walls. In some embodiments, the microfluidic devices comprise a detection module. The detection module comprises a detection electrode, a self-assembled monolayer, a binding ligand, and a detection inlet port to receive a sample.

[0009] Another embodiment of the present invention is a microfluidic device comprising a solid support. The solid support comprises a sample inlet port, a sample outlet port, and at least one microchannel comprising a gradient inducing feature coated with a magnetic material. In an embodiment, a plurality of gradient inducing features are present. In an embodiment, the gradient-inducing feature is a sawtooth ridge. In another embodiment, the gradient inducing feature is a dome. In an embodiment, the magnetic material is an iron-nickel alloy.